Rapid Construction of the Propellane Core of Acutumine via a Photochemical [2+2] Cycloaddition Reaction

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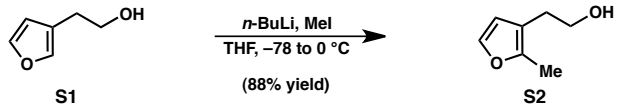
Supporting Information 1 (Experimental Procedures):

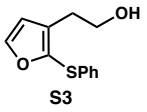
General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[1] using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^{1}H, δ = 7.26), MeCN (^{1}H, δ = 1.94), or DMSO (^{1}H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), MeCN (^{13}C, δ = 118.26), or DMSO (^{13}C, δ = 40.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Preparative HPLC was performed with an Agilent 1100 Series HPLC utilizing an Agilent Eclipse XDB-C18 5µm column (9.4 x 250 mm) or an Agilent Zorbax RX-SIL 5µm column (9.4 x 250 mm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

General procedure for the synthesis of substituted furanyl alcohol substrates:

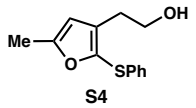


Preparation of alcohol S2. To a solution of 2-(3-furanyl)ethanol[2] (**S1**) (1.85 g, 16.5 mmol) in THF (80 mL) at –78 °C was added *n*-BuLi (2.32 M solution in hexanes, 14.2 mL, 33.0 mmol) dropwise by syringe, and the resulting solution was allowed to stir at –78 °C for 30 minutes. Upon warming to 0 °C and stirring an additional 30 minutes, methyl iodide (2.1 mL, 33.0 mmol) was added dropwise by syringe. The reaction mixture was allowed to stir 1 hour at 0 °C, then quenched by the addition of H_2O (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash chromatography (25% EtOAc in Hexanes) to afford alcohol **S2** (1.83 g, 88% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 1.4 Hz, 1H), 6.22 (d, J = 1.2 Hz, 1H), 3.74 (t, J = 6.5 Hz, 2H), 2.60 (t, J = 6.5 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 140.2, 114.9, 111.4, 62.7, 28.3, 11.5; FTIR (NaCl, thin film) 3400, 2921, 1740, 1512, 1374, 1202, 1166, 1129, 1046, 939, 893, 731 cm^{-1}; HRMS (ESI+) calc'd for $C_7H_{10}O_2$ $[M+H]^+$ 126.0681, found 126.0649.

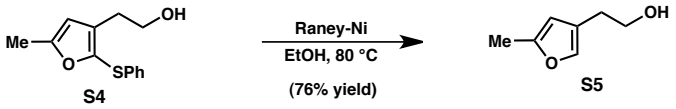
Preparation of furanyl alcohol S3. Prepared from 8.92 mmol of 2-(3-furanyl)ethanol (**S1**) using the above general procedure with diphenyl disulfide (3.89 g, 17.8 mmol) as the electrophile (added in one solid portion). The crude product was purified by flash chromatography (25% EtOAc in Hexanes) to give alcohol **S3** (1.78 g, 75% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 2.0 Hz, 1H), 7.28 – 7.21 (m, 2H), 7.21 – 7.11 (m, 1H), 7.14 – 7.06 (m, 2H), 6.50 (d, J = 2.0 Hz, 1H), 3.78 (t, J = 6.5 Hz, 2H), 2.81 (t, J = 6.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9, 140.1, 136.7, 130.2, 129.1, 126.9, 126.1, 112.9, 62.4, 29.3; FTIR (NaCl, thin film) 3338, 2947, 2879, 1582, 1478, 1440, 1142, 1067, 1024, 890, 738 cm^{-1}; HRMS (ESI+) calc'd for $C_{12}H_{12}O_2S$ $[M+H]^+$ 221.0631, found 221.0627.



Preparation of furanyl alcohol S4. Prepared from 6.81 mmol of alcohol **S3** using the above general procedure. The crude product was purified by flash chromatography (25% EtOAc in Hexanes) to give alcohol **S4** (1.43 g, 89% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 7.17 – 7.12 (m, 1H), 7.12 – 7.07 (m, 2H), 6.11 (d, J = 1.1 Hz, 1H), 3.76 (q, J = 6.2 Hz, 2H), 2.75 (t, J = 6.5 Hz, 2H), 2.32 (d, J = 1.0 Hz, 3H), 1.42 (t, J = 5.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 137.34, 137.33, 131.8, 129.0, 126.50, 125.9, 109.3, 62.5, 29.4, 14.1. FTIR (NaCl, thin film) 3338, 2947, 2923, 2878, 1605, 1583, 1478, 1440, 1248, 1116, 1048, 1024, 956, 808, 739 cm^{-1}; HRMS (ESI+) calc'd for $C_{13}H_{14}O_2S$ $[M+H]^+$ 235.0787, found 235.0791.

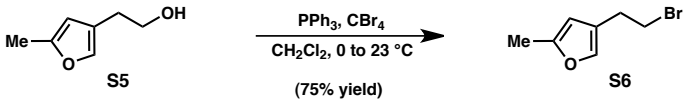


Preparation of furanyl alcohol S5.



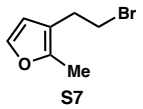
To a solution of furanyl alcohol **S4** (775 mg, 3.31 mmol) in EtOH (50 mL) was added Raney-Ni (1.50 g, 200 wt %), and the resulting suspension was heated to 80 °C. The reaction was allowed to stir a total of 2 hours and 30 minutes at 80 °C, adding additional portions of Raney-Ni (1.50 g, 200 wt %) every 30 minutes (for a total of 6 g Raney-Ni). The reaction was cooled to room temperature, filtered through a pad of Celite®, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (25% EtOAc in Hexanes) to provide alcohol **S5** (319 mg, 76% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, J = 1.0 Hz, 1H), 5.90 (t, J = 1.1 Hz, 1H), 3.75 (t, J = 6.3 Hz, 2H), 2.62 (td, J = 6.4, 0.9 Hz, 2H), 2.26 (d, J = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 138.0, 122.0, 107.0, 62.4, 28.4, 13.5. FTIR (NaCl, thin film) 3367, 2922, 2880, 1617, 1554, 1448, 1383, 1266, 1119, 1050, 1021, 920, 805 cm^{-1}; HRMS (ESI+) calc'd for $C_7H_{10}O_2$ $[M+H]^+$ 126.0681, found 126.0635.

General procedure for the synthesis of furanyl bromide substrates:

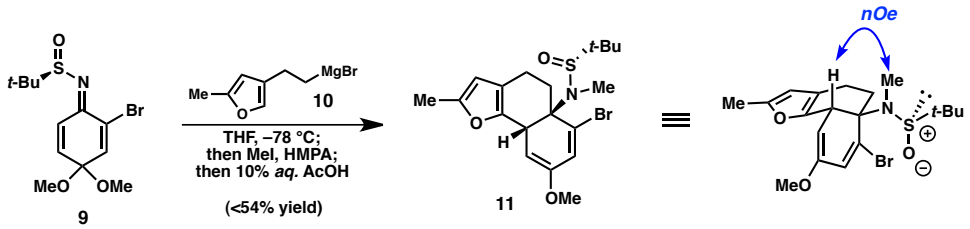


Preparation of bromide S6. To a solution of alcohol **S5** (318 mg, 2.52 mmol) and carbon tetrabromide (1.00 g, 3.02 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added triphenylphosphine (793 mg, 3.02 mmol) in one portion. The resulting solution was allowed to stir at 0 °C for 5 minutes, then warmed to room temperature and stirred an additional 30 minutes. The reaction mixture was dry loaded onto silica gel (6 g) and purified by flash chromatography (0 to 2% Et_2O in Hexanes) to give bromide **S6** (360 mg, 75% yield) as a colorless oil. Bromide **S6** proved to be a fairly unstable intermediate and was immediately converted to its corresponding Grignard reagent upon preparation.

Preparation of bromide S7. Prepared from 14.5 mmol alcohol **S2** using the above general procedure. The reaction mixture was dry loaded onto silica gel (40 g) and purified by flash chromatography (0 to 2% Et_2O in Hexanes) to give bromide **S7** (1.91 g, 70% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 1.9 Hz, 1H), 6.23 (d, J = 1.9 Hz, 1H), 3.46 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 140.2, 116.2, 111.0, 32.6, 28.9, 11.5. FTIR (NaCl, thin film) 2922, 2860, 1624, 1513, 1449, 1437, 1281, 1224, 1156, 1135, 939, 893, 731 cm^{-1}; HRMS (ESI+) calc'd for C_7H_9OBr $[M+H]^+$ 187.9837, found 187.9830.

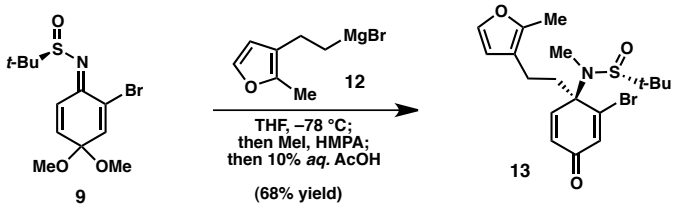


Preparation of enol ether 11.



To a solution of quinone sulfinimine **9** (71 mg, 0.21 mmol) in THF (0.4 mL) at –78 °C was added a solution of Grignard reagent[3] **10** (0.5 M solution in THF, 0.47 mL, 0.23 mmol) dropwise by syringe. The resulting solution was then stirred at –78 °C for 1 hour, then methyl iodide (39 µL, 0.63 mmol) and hexamethylphosphoramide (110 µL, 0.63 mmol) were sequentially added dropwise by syringe, and the solution stirred at –78 °C for ten minutes. The reaction was then warmed to 23 °C and stirred for 12 hours, then quenched by the addition of aqueous acetic acid (10% v/v, 0.8 mL). After 3 hours, the mixture was diluted with EtOAc (10 mL) and washed with H_2O (3 x 4 mL). The aqueous layer was back extracted with EtOAc (10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (25% to 60% EtOAc in Hexanes) to afford tricycle **11** (49 mg, 54% yield) as a pale yellow foam. The purified intermediate co-eluted with ~10% of an unidentified impurity. A small sample was further purified by preparative TLC (40% EtOAc in Hexanes) for characterization purposes: $[\alpha]_D^{25}$ +431.4° (c = 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.1 Hz, 1H), 5.75 (d, *J* = 1.1 Hz, 1H), 5.12 (dd, *J* = 6.2, 2.2 Hz, 1H), 3.82 (d, *J* = 6.2 Hz, 1H), 3.56 (s, 3H), 2.64 (dt, *J* = 13.0, 4.0 Hz, 1H), 2.58 (s, 3H), 2.56 – 2.50 (m, 1H), 2.39 (dt, *J* = 16.2, 3.7 Hz, 1H), 2.22 (s, 3H), 2.03 (ddd, *J* = 12.9, 10.6, 5.1 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 150.9, 147.3, 132.0, 127.6, 116.6, 105.6, 93.8, 66.5, 59.0, 54.8, 39.2, 32.6, 26.4, 24.6, 19.0, 13.6; FTIR (NaCl, thin film) 2952, 2922, 2863, 1657, 1577, 1453, 1362, 1251, 1218, 1175, 1072, 1024, 950, 806, 736 cm^{-1}; HRMS (ESI+) calc'd for $C_{19}H_{26}NO_3SBr$ $[M+H]^+$ 428.0897, found 428.0890.

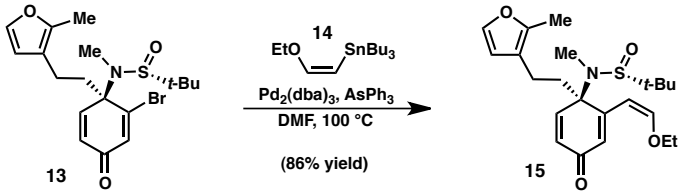
Preparation of sulfinamide 13.



To a solution of quinone sulfinimine **9** (2.22 g, 6.60 mmol) in THF (13 mL) at –78 °C was added a solution of Grignard reagent[3] **12** (0.64 M solution in THF, 12.4 mL, 7.92 mmol) dropwise by syringe. The solution was then stirred at –78 °C for 1 hour, then methyl iodide (1.2 mL, 19 mmol) and

hexamethylphosphoramide (3.3 mL, 19 mmol) were sequentially added dropwise by syringe, and the solution stirred at –78 °C for ten minutes. The solution was then warmed to 23 °C and stirred for 12 hours, then quenched by the addition of aqueous acetic acid (10% v/v, 30 mL). After 3 hours, the mixture was diluted with Et_2O (40 mL) and washed with H_2O (3 x 20 mL). The aqueous layer was back extracted with Et_2O (50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a pale brown oil. The diastereoselectivity was determined to be >98:2 by ^{1}H NMR. Flash chromatography (20% to 60% EtOAc in Hexanes) afforded dienone **13** as a pale yellow foam (1.76 g, 68% yield). $[\alpha]_D^{25}$ +6.4° (c = 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 1.8 Hz, 1H), 6.80 (d, *J* = 10.0 Hz, 1H), 6.44 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.14 (d, *J* = 1.8 Hz, 1H), 2.71 (ddd, *J* = 12.9, 11.4, 5.6 Hz, 1H), 2.46 (s, 3H), 2.16 (s, 3H), 2.13 – 2.02 (m, 2H), 1.73 (ddd, *J* = 12.9, 11.6, 5.7 Hz, 1H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 150.7, 150.0, 147.6, 140.2, 136.4, 129.7, 116.6, 111.1, 68.7, 59.2, 36.9, 26.7, 24.2, 19.5, 11.5; FTIR (NaCl, thin film) 2923, 1669, 1594, 1296, 1271, 1139, 1076, 949, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{18}H_{24}NO_3SBr$ $[M+H]^+$ 414.0733, found 414.0729.

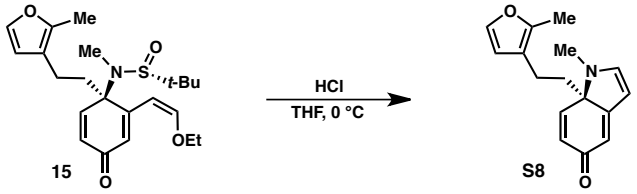
Preparation of trienone 15.



To a solution of sulfinamide **13** (1.50 g, 3.61 mmol) in DMF (20 mL) was added tris(dibenzylideneacetone)dipalladium (170 mg, 0.18 mmol), triphenylarsine (220 mg, 0.72 mmol) and *cis*-2-ethoxyvinyltributylstannane (**14**) (1.32 mL, 3.97 mmol). The solution was then thoroughly degassed with nitrogen for 30 minutes and the solution heated at 100 °C for 30 minutes. Upon cooling to room temperature, the solution was passed through a short plug of Celite, diluted with EtOAc (100 mL), and washed with H_2O (3 x 40 mL). The combined aqueous layers were back extracted with EtOAc (100 mL), and the organic layers were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a brown oil. The product was obtained as a >10:1 mixture of *Z*:*E* olefin isomers. Flash chromatography (50% to 100% EtOAc in Hexanes) afforded trienone **15** (1.26 g, 86% yield) as a tan foam. $[\alpha]_D^{25}$ –72.1° (c = 1.31, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 1.9 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 10.0 Hz, 1H), 6.36 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.09 (d, *J* = 1.8 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.08 – 3.99 (m, 2H), 2.43 (s, 3H), 2.37 (ddd, *J* = 12.7, 11.2, 5.7 Hz, 1H), 2.10 (s, 3H), 2.09 – 2.03 (m, 2H), 1.75 (ddd, *J* = 12.6, 11.2, 5.8 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 154.7, 153.5, 149.4, 147.3, 139.9, 130.5, 128.9, 117.4, 111.2, 98.7, 70.7, 66.5, 58.9, 37.2, 27.1, 24.5, 24.4, 19.5, 15.4, 11.3; FTIR (NaCl, thin

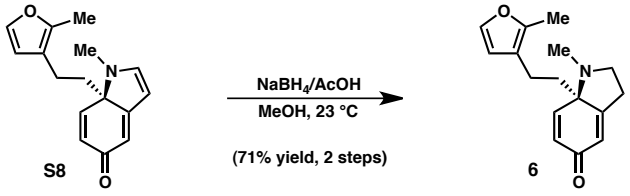
film) 2974, 2925, 1660, 1622, 1576, 1456, 1384, 1264, 1122, 1068, 954, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{22}H_{31}NO_4S$ $[M+H]^+$ 406.2047, found 406.2044.

Preparation of enamine S8.



To a solution of trienone **15** (778 mg, 1.92 mmol) in THF (38 mL) at 0 °C was added a solution of hydrogen chloride (2.0 M solution in Et_2O, 19 mL, 38 mmol) dropwise by syringe over 1 minute. The reaction was allowed to stir an additional 2 minutes at 0 °C and then quenched by the addition of aqueous NaOH (10% w/v, 25 mL). The reaction was warmed to room temperature and stirred for an additional 5 minutes. The mixture was then diluted with H_2O (10 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude enamine **S8** as a red oil, which was used immediately in the following step without further purification. A small sample was purified by flash chromatography (15 to 100% EtOAc in CH_2Cl_2) for characterization purposes: $[\alpha]_D^{25}$ –1847.5° (c = 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 1.8 Hz, 1H), 6.96 (dd, *J* = 9.8, 0.6 Hz, 1H), 6.88 (d, *J* = 3.3 Hz, 1H), 6.14 (dd, *J* = 9.8, 1.6 Hz, 1H), 6.05 (d, *J* = 1.8 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 1H), 5.45 (dd, *J* = 3.3, 0.4 Hz, 1H), 3.03 (s, *J* = 4.5 Hz, 3H), 2.20 – 2.07 (m, 2H), 2.11 (s, 3H), 1.96 – 1.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 174.5, 153.4, 147.4, 140.0, 139.9, 131.1, 116.7, 111.1, 109.8, 99.6, 72.5, 44.2, 31.5, 18.5, 11.3. FTIR (NaCl, thin film) 2918, 1630, 1568, 1516, 1314, 1246, 1138, 1088, 1041, 884, 830 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{17}NO_2$ $[M+H]^+$ 256.1332, found 256.1332.

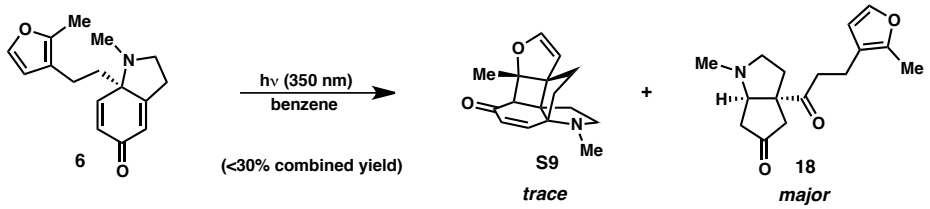
Preparation of dihydroindolone 6.



To a solution of crude enamine **S8** (1.92 mmol) in MeOH (38 mL) was added a premixed solution of $NaBH_4$ (145 mg, 3.84 mmol) in acetic acid (13 mL), dropwise by syringe. The solution was stirred at room temperature for 1 hour, then another portion of $NaBH_4$ (145 mg, 3.84 mmol) in AcOH (13 mL) was added. After stirring an additional 30 minutes, the reaction was slowly poured into a solution of KOH (50% w/v, 60 mL) at 0 °C. The mixture was then diluted and extracted with EtOAc (3 x 60 mL). The combined organic layers were dried

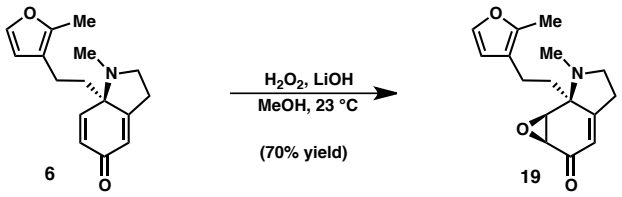
over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (50 to 100% EtOAc in CH_2Cl_2) to afford dihydroindolone **6** (349 mg, 71% yield, 2 steps) as a red oil. $[\alpha]_D^{25}$ +54.6° (c = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 10.0 Hz, 1H), 6.32 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.18 (dt, *J* = 3.3, 1.6 Hz, 1H), 6.10 (d, *J* = 1.9 Hz, 1H), 3.17 (ddd, *J* = 10.5, 8.3, 4.6 Hz, 1H), 3.07 – 2.99 (m, 1H), 2.77 – 2.69 (m, 2H), 2.40 (s, 3H), 2.16 – 2.05 (m, 1H), 2.12 (s, 3H), 1.99 (ddd, *J* = 14.1, 11.2, 5.8 Hz, 1H), 1.81 – 1.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 166.9, 147.2, 145.9, 140.0, 130.2, 123.3, 117.5, 111.0, 66.4, 51.5, 36.4, 30.6, 27.8, 19.1, 11.4. FTIR (NaCl, thin film) 2919, 2849, 1669, 1643, 1607, 1512, 1452, 1272, 1176, 1139, 892, 732 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_2$ $[M+H]^+$ 258.1489, found 258.1490.

Photochemical [2+2] reaction of dihydroindolone 6.



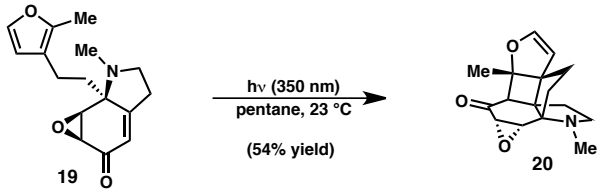
A solution of dihydroindolone **6** (70 mg, 0.27 mmol) in benzene (36 mL) was divided into six 6 mL portions, which were each placed in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 2 hours, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (1 to 3% MeOH in CH_2Cl_2) to give a mixture of dihydrofuran **S9**, diketone **18**, and small amounts (~10%) of other unidentified products (21 mg total, <30% yield). This mixture of products was further purified by preparative TLC for characterization purposes. Spectral data[5] for dihydrofuran **S9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 10.5 Hz, 1H), 6.43 (d, *J* = 2.9 Hz, 1H), 6.07 (d, *J* = 10.5 Hz, 1H), 4.84 (d, *J* = 2.9 Hz, 1H), 3.29 (s, 1H), 2.67 (dt, *J* = 8.7, 6.7 Hz, 1H), 2.58 (dt, *J* = 9.0, 6.9 Hz, 1H), 2.47 (s, 3H), 2.36 – 2.22 (m, 2H), 1.89 – 1.78 (m, 1H), 1.78 – 1.63 (m, 3H), 1.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4, 151.5, 147.0, 128.7, 103.5, 89.0, 70.5, 66.9, 61.5, 57.1, 54.3, 35.8, 34.6, 32.2, 28.8, 16.3. Characterization data for diketone **18**: $[\alpha]_D^{25}$ +45.1° (c = 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.9 Hz, 1H), 6.13 (d, *J* = 1.9 Hz, 1H), 3.16 (ddd, *J* = 9.3, 8.0, 1.2 Hz, 1H), 2.89 (d, *J* = 18.6 Hz, 1H), 2.85 (d, *J* = 5.6 Hz, 1H), 2.78 – 2.62 (m, 4H), 2.42 (td, *J* = 9.7, 8.2 Hz, 1H), 2.35 – 2.15 (m, 4H), 2.26 (s, 3H), 2.20 (s, 3H), 1.88 (ddd, *J* = 13.4, 9.8, 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 209.7, 147.8, 140.2, 117.2, 111.1, 69.2, 62.2, 56.7, 47.3, 41.9, 39.7, 38.9, 34.9, 19.5, 11.4; FTIR (NaCl, thin film) 2919, 2848, 2785, 1745, 1700, 1513, 1452, 1395, 1351, 1252, 1138, 1045, 893, 735 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_3$ $[M+H]^+$ 276.1594, found 276.1591.

Preparation of epoxide 19.



To a solution of dienone **6** (213 mg, 0.828 mmol) in methanol (8 mL) was added LiOH (40.0 mg, 1.66 mmol), followed by aqueous H_2O_2 (101 μL of a 50 wt % solution in H_2O, 1.66 mmol). The resulting solution was allowed to stir at room temperature for 1 hour, then H_2O (8 mL) was added. The reaction mixture was extracted with EtOAc (3 x 20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (50 to 75% EtOAc in Hexanes) to provide epoxide **19** (158 mg, 70% yield) as a yellow oil. $[\alpha]_D^{25}$ –235.9° (c = 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.9 Hz, 1H), 6.13 (d, *J* = 1.8 Hz, 1H), 5.87 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.62 (d, *J* = 4.1 Hz, 1H), 3.42 (dd, *J* = 4.1, 1.8 Hz, 1H), 3.15 (ddd, *J* = 9.4, 7.7, 4.6 Hz, 1H), 2.85 (td, *J* = 9.3, 6.6 Hz, 1H), 2.74 – 2.66 (m, 2H), 2.56 (s, 3H), 2.20 – 2.05 (m, 5H), 1.84 (ddd, *J* = 13.8, 11.3, 5.8 Hz, 1H), 1.74 (ddd, *J* = 13.9, 12.0, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.0, 162.6, 147.2, 140.1, 118.5, 117.3, 110.8, 65.4, 53.5, 53.3, 50.9, 35.0, 29.7, 28.5, 19.5, 11.4. FTIR (NaCl, thin film) 2918, 2848, 1676, 1512, 1448, 1273, 1171, 1137, 1055, 893 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.

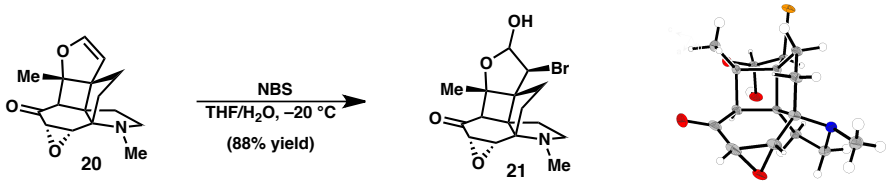
Preparation of dihydrofuran 20.



A solution of enone **19** (38 mg, 0.14 mmol) in a 50:1 mixture of pentane/benzene (24 mL) was divided into four 6 mL portions, which were each placed in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 50 minutes, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (50 to 75% EtOAc in Hexanes) to give dihydrofuran **20** (20 mg, 52% yield) as a pale yellow solid, as well as unreacted epoxide **19** (7 mg, 65% yield brsm). $[\alpha]_D^{25}$ +55.1° (c = 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 4.65 (d, *J* = 2.8 Hz, 1H), 3.64 (d, *J* = 4.3 Hz, 1H), 3.24 (d, *J* = 4.3 Hz, 1H), 3.18 (s, 1H), 2.97 (td, *J* = 8.6, 5.6 Hz, 1H), 2.77 (ddd, *J* = 8.5, 7.7, 5.6 Hz, 1H), 2.48 (s, 3H), 2.31 (ddd, *J* = 13.1, 7.6, 5.7 Hz, 1H), 2.11 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.95 (ddd, *J* = 13.4, 8.4, 5.6 Hz, 1H), 1.84 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.74 (td, *J* = 13.3, 7.6 Hz, 1H), 1.56 (td, *J* = 13.3, 7.6 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 147.4, 103.0, 89.0, 71.0, 65.5, 62.1, 60.0, 55.8, 55.7, 54.6, 34.6, 32.0,

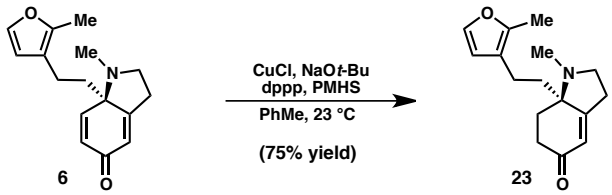
31.6, 29.8, 16.8. FTIR (NaCl, thin film) 2949, 2930, 2889, 2786, 1699, 1606, 1448, 1187, 1136, 1027, 883, 872 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.

Preparation of bromohydrin 21.



To a solution of dihydrofuran **20** (19 mg, 0.070 mmol) in a 10:1 mixture of THF:H_2O (1.4 mL total) at –20 °C was added *N*-bromosuccinimide (13 mg, 0.075 mmol). The reaction mixture was allowed to stir 30 minutes at –20 °C and then quenched with saturated aqueous sodium thiosulfate (2 mL). After stirring for 10 min and warming to room temperature, the mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (30 to 40% EtOAc in Hexanes) to furnish bromohydrin **21** (23 mg, 88% yield) as a white solid. $[\alpha]_D^{25}$ –7.5° (c = 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3:1 mixture of inseparable diastereomers, major diastereomer is designated by *, minor diastereomer denoted by §) δ 5.85 (s, 1H*), 5.14 (s, 1H§), 4.45 (s, 1H§), 4.44 (s, 1H*), 3.65 (d, *J* = 4.5 Hz, 1H§), 3.64 (d, *J* = 4.4 Hz, 1H*), 3.31 (s, 1H*), 3.23 (d, *J* = 4.4 Hz, 1H§), 3.21 (d, *J* = 4.3 Hz, 1H*), 3.03 – 2.98 (t, *J* = 6.9 Hz, 2H§), 2.97 – 2.91 (m, 1H*), 2.97 – 2.91 (m, 2H§), 2.54 (dt, *J* = 14.6, 7.4 Hz, 1H*), 2.49 (s, 3H*), 2.48 (s, 3H§), 2.20 – 2.06 (m, 1H*, 2H§), 2.06 – 1.98 (m, 2H*, 2H§), 1.93 (ddd, *J* = 14.3, 7.6, 5.4 Hz, 1H*), 1.44 (ddd, *J* = 14.0, 12.8, 7.5 Hz, 1H*), 1.39 (ddd, *J* = 14.1, 12.9, 7.4 Hz, 1H§), 1.29 (s, 3H*, 3H§), 0.88 (m, 1H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8*, 203.9§, 106.5*, 95.6§, 89.2*, 83.9§, 73.54*, 73.48§, 64.4*, 63.5*, 63.0§, 58.6*, 58.1§, 57.6§, 57.0*, 56.3*, 56.1§, 55.1§, 54.58§, 54.57*, 54.51*, 54.3§, 34.5*, 34.3§, 32.8*, 32.0*, 31.8§, 30.02§, 29.96*, 29.87§, 18.8*, 18.2§. FTIR (NaCl, thin film) 3413, 2937, 2854, 1701, 1449, 1379, 1255, 1215, 1177, 1021, 930, 877, 737 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{20}NO_4Br$ $[M+H]^+$ 370.0648, found 370.0641.

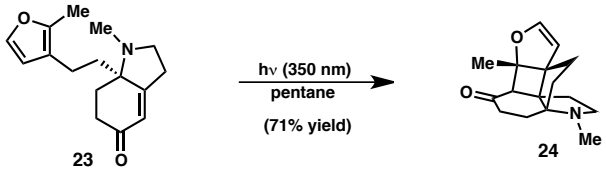
Preparation of enone 23.



In a glove box, a round bottom flask was charged with copper (I) chloride (8.6 mg, 0.087 mmol), NaO*t*-Bu (8.4 mg, 0.087 mmol), 1,3-bis(diphenylphosphino)propane (36 mg, 0.087 mmol), and degassed PhMe (5.7 mL), and the mixture was stirred vigorously for 20 minutes. The reaction was brought out onto the benchtop,

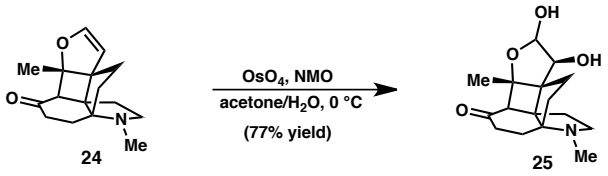
placed under an atmosphere of nitrogen, and polymethylhydrosiloxane (58 μL, 0.96 mmol) was added, followed by a solution of dienone **6** (225 mg, 0.87 mmol) in degassed PhMe (3 mL). The reaction was allowed to stir 2 hours, then quenched by the addition of aqueous 1 N NaOH (9 mL) and stirred vigorously for 20 minutes. The resulting mixture was diluted and extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0 to 3% MeOH in CH_2Cl_2) to give enone **23** (170 mg, 75% yield) as a yellow oil. $[\alpha]_D^{25}$ –115.9° (c = 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.8 Hz, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.87 – 5.83 (m, *J* = 1.5 Hz, 1H), 3.02 – 2.92 (m, 2H), 2.73 (dddd, *J* = 17.7, 8.1, 5.9, 2.3 Hz, 1H), 2.65 (dddd, *J* = 17.8, 7.4, 5.9, 1.4 Hz, 1H), 2.49 – 2.41 (m, 3H), 2.46 (s, 3H), 2.41 – 2.30 (m, 1H), 2.25 (ddd, *J* = 12.8, 5.0, 2.4 Hz, 1H), 2.19 (s, 3H), 1.87 (td, *J* = 13.0, 7.0, 1H), 1.82 (ddd, *J* = 14.2, 12.4, 4.8 Hz, 1H), 1.68 (ddd, *J* = 14.3, 12.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 172.7, 147.0, 140.0, 121.5, 118.4, 111.0, 63.2, 51.7, 35.0, 33.6, 33.3, 31.6, 30.3, 21.4, 11.5; FTIR (NaCl, thin film) 2923, 2784, 1669, 1448, 1270, 1198, 1137, 892, 729 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1645, found 260.1645.

Preparation of dihydrofuran 24.



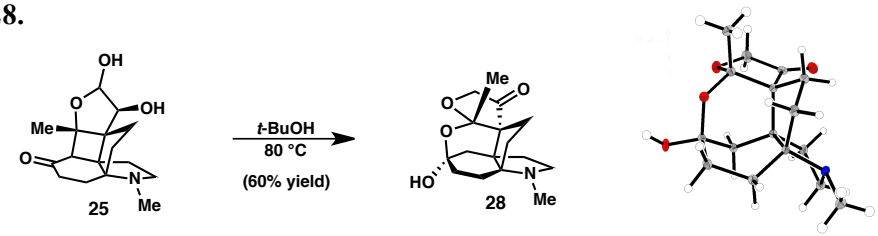
A solution of enone **23** (170 mg, 0.66 mmol) in a 50:1 mixture of pentane/benzene (65 mL) was divided into ten 6.5 mL portions, which were each placed in 13x100 mm borosilicate test tubes. The reaction tubes were irradiated in a Luzchem photoreactor fitted with λ ≈ 350 nm lamps and a merry-go-round apparatus. After irradiating for 6 hours, the reaction mixtures were combined and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2 to 8% MeOH in CH_2Cl_2) to give dihydrofuran **24** (120 mg, 71% yield) as a pale yellow solid. $[\alpha]_D^{25}$ +207.6° (c = 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.8 Hz, 1H), 4.74 (d, *J* = 2.8 Hz, 1H), 3.10 (s, 1H), 2.76 – 2.65 (m, 2H), 2.52 – 2.43 (m, 1H), 2.35 – 2.23 (m, 2H), 2.28 (s, 3H), 1.97 – 1.84 (m, 3H), 1.83 – 1.72 (m, 3H), 1.64 (ddd, *J* = 13.9, 8.2, 6.7 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 146.6, 104.1, 88.5, 71.1, 65.3, 62.3, 60.2, 53.0, 37.0, 34.5, 31.5, 30.7, 29.6, 24.1, 16.9; FTIR (NaCl, thin film) 2925, 2864, 2783, 1696, 1600, 1457, 1379, 1169, 1139, 1031, 879, 755 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{21}NO_2$ $[M+H]^+$ 260.1645, found 260.1644.

Preparation of diol 25.



To a solution of dihydrofuran **24** (93 mg, 0.36 mmol) in acetone (6.4 mL) at 0 °C was added osmium tetroxide (23 µL of a 4 wt % solution in H_2O, 3.6 µmol), followed by a solution of *N*-methylmorpholine-*N*-oxide (46 mg, 0.39 mmol) in H_2O (0.6 mL). The resulting solution was allowed to stir 45 minutes at 0 °C. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (6 mL), and the resulting mixture was stirred at 0 °C for 20 minutes. The biphasic mixture was warmed to room temperature and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (5 to 20% MeOH in CH_2Cl_2) to provide diol **25** (81 mg, 77% yield) as an off-white foam. $[\alpha]_D^{25}$ +116.4° (c = 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2:1 mixture of inseparable diastereomers[4], major diastereomer is designated by *, minor diastereomer denoted by §) δ 5.50 (s, 1H§), 5.37 (d, *J* = 2.9 Hz, 1H*), 4.23 (s, 1H§), 3.92 (d, *J* = 2.8 Hz, 1H*), 3.30 (s, 1H§), 2.99 – 2.82 (m, 1H*, 1H§), 2.85 (s, 1H*), 2.79 (td, *J* = 9.3, 6.0 Hz, 1H*), 2.76 – 2.69 (m, 1H§), 2.60 – 2.54 (m, 1H§), 2.54 – 2.45 (m, 1H*, 1H§), 2.37 – 2.20 (m, 2H*, 1H§), 2.32 (s, 3H§), 2.31 (s, 3H*), 2.18 (ddd, *J* = 14.1, 8.2, 6.0 Hz, 1H*), 1.97 – 1.82 (m, 3H*, 3H§), 1.82 – 1.71 (m, 2H*, 2H§), 1.71 – 1.59 (m, 1H*, 1H§), 1.20 (s, 3H*, 3H§); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.6§, 209.3*, 106.1§, 97.7*, 88.3§, 84.3*, 79.4§, 74.0*, 73.3§, 72.8*, 64.6§, 62.5*, 61.7§, 59.8*, 54.9§, 54.1*, 53.0§, 52.9*, 36.31§, 36.27*, 34.7§, 34.6*, 31.4§, 30.0*, 29.7§, 29.1*, 29.0§, 26.1*, 22.2*, 21.8§, 18.8§, 18.6*. FTIR (NaCl, thin film) 3369, 2935, 2864, 2788, 1691, 1448, 1183, 1146, 1125, 1049, 1022, 979, 914, 875, 754 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{23}NO_4$ $[M+H]^+$ 294.1700, found 294.7001.

Preparation of ketal 28.



A 20-mL vial was charged with diol **25** (30 mg, 0.10 mmol) and *t*-BuOH (3 mL), sealed, and heated to 80 °C for 5 days. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2 to 8% MeOH in CH_2Cl_2) to give ketal **28** (18 mg, 60% yield) as a pale yellow solid. $[\alpha]_D^{25}$ +47.9° (c = 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, *J* = 17.7 Hz, 1H), 3.90 (d, *J* = 17.7 Hz, 1H), 2.97 (s, 1H), 2.88 (q, *J* = 8.6 Hz, 1H), 2.67 (td, *J* = 9.5, 2.3 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.25 (s, 3H), 2.18 (dd, *J* = 13.4, 1.7 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.93 (d, *J* = 13.4 Hz, 1H), 1.88 – 1.71 (m, 3H), 1.69 – 1.61 (m, 2H), 1.59 – 1.49 (m, 1H), 1.42 – 1.36 (m, 1H), 1.35 (s, 3H), 1.04 (ddd, *J* = 12.7, 7.1,

2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 109.8, 97.3, 73.1, 69.2, 60.4, 55.4, 51.2, 36.2, 35.2, 34.1, 31.3, 29.4, 26.6, 24.3, 24.2. FTIR (NaCl, thin film) 3066, 2966, 2938, 2804, 1744, 1452, 1353, 1313, 1240, 1185, 1129, 1074, 1055, 1002, 900, 876, 859 cm^{-1}; HRMS (ESI+) calc'd for $C_{16}H_{23}NO_4$ $[M+H]^+$ 294.1700, found 294.1705.

References

[1] Still, W. C., Kahn, M. & Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

[2] 2-(3-furanyl)ethanol was prepared according to following literature procedure, with a slight modification to the hydroboration step: BH_3•Me_2S was substituted for 9-BBN. See: Hersel, U.; Steck, M.; Seifert, K. *Eur. J. Org. Chem*. **2000**, 1609-1615.

[3] Grignard reagent **12** was prepared as follows: To a suspension of magnesium turnings (1.60 g, 65.8 mmol) in THF (8 mL) was added diisobutylaluminum hydride (60 μL, 0.34 mmol). The resulting suspension was heated to reflux, and a solution of bromide **S7** (7.58 g, 40.1 mmol) in THF (42 mL) was added dropwise. The reaction was maintained at reflux for 1 hour, then cooled to room temperature. The resulting Grignard reagent was titrated and stored in a Schlenk tube.

[4] During the course of collecting the ^{13}C NMR data for diol **25**, this intermediate slowly undergoes retro-aldol/intramolecular ketalization to give the corresponding ketal (**28**). The carbon signals corresponding to **28** are noted in the carbon spectrum of **25** (see Supporting Information 2).

[5] Less than 1 mg of analytically pure dihydrofuran **S9** was isolated; as such, some carbon signals were extrapolated from HMBC spectral data. See Supporting Information 2.